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REVIEW

Emerging systemic JAK inhibitors in the treatment of atopic dermatitis: a review of abrocitinib, baricitinib, and upadacitinib

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Abstract

The Janus kinases (JAK) are a group of molecules, composed of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), which are key components within the JAK–signal transducers and activators of transcription pathway, where cytokine receptor signaling takes place. These molecules play a foundational role in the underlying pathogenesis of multiple immune-related conditions such as atopic dermatitis (AD), rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, and others. Thus far, JAK inhibitors for inflammatory conditions have only been marketed for the treatment of rheumatoid arthritis and psoriatic arthritis, but ongoing phase II and phase III clinical trials for other immune-mediated diseases, such as AD, have also shown promising results. This review summarizes the clinical data available from various trials and reports on the safety and efficacy of abrocitinib, baricitinib, and upadacitinib, the three oral systemic JAK inhibitors used in the treatment of AD. The safety and efficacy of JAK inhibitors for the treatment of AD are emerging in the literature. It is important that dermatologists are aware of any potential adverse events or risks associated with the use of JAK inhibitors in order to promote a higher standard of treatment and quality of living.

Keywords: abrocitinib, atopic dermatitis, baricitinib, eczema, JAK1, JAK2, JAK inhibitors, upadacitinib.

Citation

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Introduction

The Janus kinase–signal transducers and activators of transcription (JAK–STAT) pathway is one of the key components in the pathogenesis of multiple immune-mediated conditions, including rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, and atopic dermatitis (AD). Various proinflammatory cytokines are able to exert their pathophysiologic function through this intracellular signaling pathway.[1]

The JAK family is composed of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2).[2] JAK inhibitors target the various kinases, causing a suppression in the activity of one or more of these targets.[3] A growing body of literature has demonstrated that JAK inhibitors are safe and efficacious in multiple inflammatory skin conditions, extending the investigation of JAK inhibitors as a treatment for AD.[4]

The first generation of JAK inhibitors include tofacitinib, ruxolitinib, baricitinib, and oclacitinib,[4] all of which are approved by the FDA for use in humans, except for oclacitinib, which is approved for veterinary use.[5] Second-generation agents have an increased selectivity to certain JAK isoforms; abrocitinib and upadacitinib are commonly referred to as 'selective JAK1 inhibitors' as they have greater selectivity to JAK1 compared to the other isoforms (see Table 1 for the IC_{50} of each agent). They are both currently under investigation for the systemic treatment of AD. As JAK inhibitors are small molecules, in addition to being administered orally, they are also amenable to topical application and are currently being investigated in this format with ruxolitinib and delgocitinib (Table 2).[6]

The aim of this narrative review is to address the oral systemic JAK inhibitors abrocitinib, baricitinib, and upadacitinib in the treatment of moderate-to-severe AD. This article is based on available data from previously conducted clinical trials (Table 3). PubMed, ClinicalTrials.gov, and other scholarly journals were explored as search engines. We used the terms 'atopic dermatitis,' 'JAK inhibitors,' 'abrocitinib,' 'baricitinib,' and 'upadacitinib' and searched between January 2020 and May 2020 to find the appropriate articles in the literature. We included randomized controlled trials and excluded case reports, case series, or review articles.

Table 1. IC_{50} values for the inhibition of JAK1, JAK2, JAK3, and TYK2 for abrocitinib, upadacitinib, and baricitinib.

	IC_{50} values (nM)			
	JAK1	JAK2	JAK3	TYK2
Abrocitinib[26]	29	803	>10,000	1250
Upadacitinib[27]	45	109	2100	4700
Baricitinib[28]	5.9	5.7	>400	53

Table 2. Current JAK inhibitors being investigated for atopic dermatitis.

Drug	Other names	Main target	Format
Abrocitinib	PF-04965842	JAK1	Oral
Upadacitinib	Rinvoq[a]	JAK1	Oral
Baricitinib	Olumiant[b]	JAK1, JAK2	Oral
Oclacitinib	Apoquel[b]	JAK1	Oral (veterinary)
Ruxolitinib	Jakafi[b] and Jakavi[b]	JAK1, JAK2	Topical
Delgocitinib	JTE-052	Pan-JAK	Topical

[a]Trademark, [b]Registered trademark.

Pathogenesis of atopic dermatitis

AD, also known as atopic eczema, is a chronic inflammatory skin condition characterized by pruritic, xerotic, and inflamed skin. This heterogeneous condition has a complex pathophysiology with clinical manifestation through the presentation of various signs and symptoms, as recently reviewed.[7] It negatively impacts on the quality of life of those living with the condition and, due to its chronic nature, ongoing treatment is often needed. Although mild atopic dermatitis is typically managed with topical therapy, moderate-to-severe disease often requires systemic therapy. AD develops in individuals with a genetic predisposition and exogenous provocation factors.[7] AD often begins in childhood, with approximately 60% of patients developing AD prior to the age of 1 year, 90% by the age of 5 years, and 10% may develop AD as adults.[8]

JAK–STAT inhibition in AD

Several cytokines that signal *via* the JAK–STAT pathway play an essential role in the pathophysiology of inflammatory skin diseases, including AD.[9,10] The JAK–STAT signaling pathway is one of the several signal-transduction pathways fundamental for various homeostatic and developmental processes and has been recognized as a target for the inhibition of cytokines.[11]

JAK1, JAK2, and TYK2 are omnipresent in mammals.[12] In contrast, JAK3 is more restricted in its expression, associated mainly with hematopoietic cells,[12] thus being highly controlled by cell development and activation.[12]

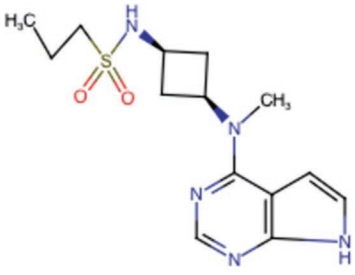
The individual JAK proteins are selective in their association with different receptors; however, as only four exist, each is used by a number of different receptors for a range of biological purposes.[12] JAK1 is essential for granulocyte colony-stimulating factor, which stimulates the production of granulocytes and stem cells, and interferons.[12] JAK activation induces cell migration, differentiation, cell proliferation, and apoptosis. Therefore, the therapeutic inhibition of JAK–STAT proteins by small-molecule inhibitors impedes immune cell function by detaching cells from cytokine effects and by interfering with functional immune cell hallmarks, such as cell migration.[13] Therefore, JAK inhibitors exert immunomodulatory and antiproliferative effects.[14] JAK1 plays an important role in the expression of IL-4, IL-5, IL-13, and IL-31, all of which are associated with the pro-inflammatory signaling pathways of AD.[15] Aside from AD, other skin disorders associated with JAK1 activity include psoriasis, alopecia areata, and vitiligo.[4,16] Currently, there are no approved JAK inhibitors for the treatment of dermatological diseases.[10] This paper reviews the JAK inhibitors under investigation: abrocitinib, baricitinib, and upadacitinib (their molecular structures are provided in Figure 1).

Table 3. Phase II and III registered studies with JAK inhibitors for treatment of atopic dermatitis.

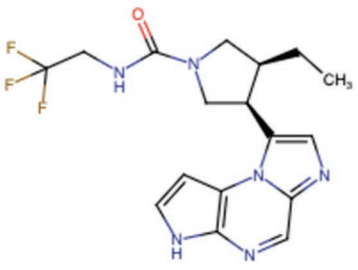
ClinicalTrials.gov identifier	Interventions	Phase	Status at time of publication
Abrocitinib[29]			
NCT02780167	Abrocitinib, placebo	II	Completed, has results
NCT04345367	Abrocitinib, dupilumab	III	Recruiting
NCT03422822	Abrocitinib, placebo	III	Recruiting
NCT03627767	Abrocitinib, placebo	III	Active, not recruiting
NCT03796676	Abrocitinib, placebo	III	Completed
NCT03720470	Abrocitinib, dupilumab, placebo	III	Completed
NCT03575871	Abrocitinib, placebo	III	Completed, has results
NCT03349060	Abrocitinib, placebo	III	Completed, has results
Baricitinib[30]			
NCT02576938	Baricitinib, placebo, TCS	II	Completed, has results
NCT03334422	Baricitinib, placebo	III	Completed, has results
NCT03334435	Baricitinib, placebo	III	Active, not recruiting
NCT03559270	Baricitinib	III	Enrolling by invitation
NCT03334396	Baricitinib, placebo	III	Completed, has results
NCT03952559	Baricitinib, placebo, TCS	III	Recruiting
NCT03435081	Baricitinib, placebo	III	Active, not recruiting
NCT03733301	Baricitinib, placebo, TCS	III	Completed, has results
NCT03428100	Baricitinib, placebo, TCS	III	Active, not recruiting
Upadacitinib[31]			
NCT02925117	Upadacitinib, placebo	II	Completed, has results
NCT03569293	Upadacitinib, placebo	III	Active, not recruiting
NCT03568318	Upadacitinib, placebo, TCS	III	Recruiting
NCT03661138	Upadacitinib, placebo, TCS	III	Active, not recruiting
NCT04195698	Upadacitinib	III	Enrolling by invitation
NCT03607422	Upadacitinib, placebo	III	Recruiting
NCT03738397	Upadacitinib, placebo, dupilumab	III	Active, not recruiting

TCS, topical corticosteroids.

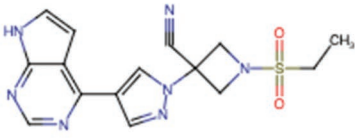
Figure 1. Chemical structures of abrocitinib, baricitinib, and upadacitinib.



Abrocitinib



Upadacitinib



Baricitinib

Efficacy of JAK inhibitors in AD

JAK1-selective inhibitors

Abrocitinib

Abrocitinib (PF-04965842), an orally administered selective JAK1 inhibitor, is under investigation for the treatment of AD. According to a phase II, randomized, double-blinded, placebo-controlled, parallel-group study on 267 adult patients with moderate-to-severe AD,[17] once daily (QD) oral abrocitinib was effective and well tolerated. Patients were randomly assigned to receive abrocitinib, 200 mg, 100 mg, 30 mg, 10 mg, or placebo for 12 weeks. At 12 weeks, 43.8% of patients receiving 200 mg abrocitinib, 29.6% of patients receiving 100 mg abrocitinib, and 5.8% of patients receiving placebo improved 2 grades or more with clear (0) or almost clear (1) on the Investigator's Global Assessment (IGA) scale (also known as an IGA response). Furthermore, significant reductions in pruritus scores were reported at week 12 in the treatment groups receiving 200 mg and 100 mg abrocitinib. Improvements in Eczema Area and Severity Index (EASI) scores and body surface area percentage reductions were observed as early as week 1 of treatment.

The safety and efficacy of abrocitinib were recently evaluated in the two identical phase III JADE MONO-1 and JADE MONO-2 trials. At week 12, 43.8%, 23.7%, and 7.9% of those participants receiving 200 mg abrocitinib, 100 mg abrocitinib, and placebo, respectively, achieved an IGA response in the JADE-MONO-1 study,[18] whereas the IGA response was 38.1%, 28.4%, and 9.1%, respectively, in the JADE MONO-2 trial.[19] According to the JADE MONO-1 study, an improvement of at least 75% in EASI score (EASI-75) was reached in 62.7%, 39.7%, and 11.8% of those treated with 200 mg, 100 mg, and placebo, respectively, whereas EASI-75 was achieved in 61.0%, 44.5%, and 10.4% of participants receiving 200 mg, 100 mg, and placebo, respectively, in the JADE MONO-2 study. At week 12, a Peak Pruritus Numerical Rating Scale score improvement of 4 or more was achieved in 57%, 38%, and 15% of those participants receiving 200 mg abrocitinib, 100 mg abrocitinib, and placebo, respectively, in the JADE MONO-1 study and in 55.3%, 45.2%, and 11.5% of participants in the JADE MONO-2 study. In both JADE MONO studies, improvements in EASI-75 and IGA were reported as early as 2 weeks of treatment. According to the results of these trials, abrocitinib met all co-primary and secondary endpoints, leading to skin clearance and relief of pruritus.

Upadacitinib

Upadacitinib (ABT-494) is another selective inhibitor of JAK1 undergoing clinical trials to determine its benefit for several inflammatory diseases, including AD.[20] A phase II double-blinded, placebo-controlled, parallel-group, dose-ranging study of upadacitinib included 167 patients with moderate-to-severe AD who received a daily dose of 7.5, 15, or 30 mg oral upadacitinib or placebo for 16 weeks.[21] The study was part of a longer 88-week, eight-country trial.[21] At week 16, all three treatment arms showed significant benefits compared to placebo, while 30 mg upadacitinib provided the maximum clinical benefits.[21] Half of the patients receiving the 30 mg dose of upadacitinib achieved clear or almost clear skin based on the IGA score and an improvement of at least 90% in EASI at week 16.[22] Improvements in signs and symptoms of AD were shown after the first week in those receiving upadacitinib (7.5, 15, 30 mg), with a significant reduction in pruritus as well as clinical efficacy end points.[21]

JAK1 and JAK2 inhibitors

Baricitinib

Baricitinib is a first-generation inhibitor of JAK1 and JAK2 and is furthest along the development pathway for treatment of moderate-to-severe AD. The results of a phase II trial by Guttman-Yassky et al.[23] published in early 2019, highlighted the benefits of this drug for the treatment of AD; further phase III trials have also been completed.[24] The phase II randomized, 16-week, double-blinded, placebo-controlled study reported the efficacy and safety of baricitinib in combination with topical corticosteroids in adult patients with moderate-to-severe AD.[23] Of the 187 patients screened, 124 were successfully enrolled and randomized in a 4:3:3 ratio, corresponding to QD placebo or 2 or 4 mg baricitinib. Subjects who received 4 mg baricitinib achieved a significant improvement of at least 50% in EASI compared to patients who had received placebo (61% *versus* 37%, respectively) at 16 weeks. It was reported that baricitinib also improved sleep loss and pruritus.

Recently, results from two identical randomized monotherapy phase III trials, BREEZE-AD1 and BREEZE-AD2, have been published.[24] In these trials, adults with moderate-to-severe AD were randomized to QD baricitinib, 1, 2, 4 mg, or placebo for a total of 16 weeks. After 16 weeks, more patients had achieved the primary endpoint of IGA 0/1 in both baricitinib 2 mg (11.4%) and 4 mg (16.8%) treatment arms compared to placebo (4.8%) in both the BREEZE-AD1 and BREEZE-AD2 trials. Baricitinib 4 mg provided a significant improvement in EASI score, with a 59.4% and 54.9% reduction in BREEZE-AD1 and BREEZE-AD2, respectively, at week 16. Patients also reported an improvement in itch as early as the first week using baricitinib 4 mg and as early as the second week for 2 mg. Additionally, patients in both the baricitinib 4 mg and 2 mg groups noted improvements in skin pain, quality-of-life measures, and nighttime waking during the first week.

Safety of JAK inhibitors in AD

Abrocitinib

The phase IIb trial of 267 adult patients with moderate-to-severe AD[17] reported dermatitis atopic, headache, nausea, upper respiratory tract infection, and diarrhea as the most frequent treatment-emergent adverse events (TEAEs). Serious adverse events (SAEs) included one case of pneumonia and one case of pulmonary embolism in the 200 mg abrocitinib group as well as one case each of asthma, aggravation of dermatitis, and eczema herpeticum in the 100 mg abrocitinib

group.[17] Reductions in platelet counts were observed in the 200 mg abrocitinib and 100 mg abrocitinib groups; however, these reached toward normalization after 4 weeks of continued treatment and were not associated with any clinical sequelae.

Recently, results from the phase III JADE MONO-1 and JADE MONO-2 trials, which included both adolescents and adults with AD, were presented. In the JADE MONO-1 trial, among 387 subjects, SAEs were reported in 3.2%, 3.2%, and 3.9% of patients in the 200 mg abrocitinib, 100 mg abrocitinib, and placebo treatment groups, respectively.[18] There were no cases of thromboembolism or any deaths. TEAEs were reported in 77.9%, 69.2%, and 57.1% of the 200 mg abrocitinib, 100 mg abrocitinib, and placebo groups, respectively. According to the JADE MONO-2 study,[19] of 391 subjects, SAEs were reported in 1.3%, 3.2%, and 1.3% of patients in the 200 mg abrocitinib, 100 mg abrocitinib, and placebo groups, respectively, with one sudden cardiac death reported in the 100 mg abrocitinib group occurring during the follow-up period and was deemed not to be related to treatment. TEAEs were reported in 65.8%, 62.7%, and 53.8% of patients in the 200 mg abrocitinib, 100 mg abrocitinib, and placebo treatment arms, respectively.[19] In both the JADE MONO-1 and JADE MONO-2 trials, the most common TEAEs were headache, nausea, nasopharyngitis, upper respiratory tract infection, and AD. Platelet count reductions as well as lipid level elevations were reported in both JADE MONO-1 and JADE MONO-2. Although platelets reduced with a nadir at week 4, levels trended towards baseline despite ongoing therapy. In addition to these TEAEs, vomiting and acne were reported as the more frequent TEAEs in the JADE MONO-2 trial.[19] Overall, according to the phase II and III trials, abrocitinib may be a safe alternative to conventional AD therapies.

Upadacitinib

The phase IIb clinical trial of 166 randomized participants reported no deaths and 0, 1, and 2 SAEs in the 30, 15, and 7.5 mg upadacitinib groups, respectively, *versus* 1 SAE in the placebo group.[21] The most common adverse effects (AEs) (10% or greater in each treatment group) included upper respiratory tract infection, worsening of acne, and AD. However, there was no correlation between the occurrence of AEs and dose of upadacitinib. Therefore, there were no safety concerns to preclude further investigation of upadacitinib for AD, and phase III trials are currently under way.

Baricitinib

In the phase II trial conducted to assess the safety and efficacy of baricitinib in 124 adult patients with AD, TEAEs were reported in 49%, 46%, and 71% of the participants in the placebo group, those receiving 2 mg baricitinib, and those receiving 4 mg baricitinib, respectively. Overall, baricitinib indicated a safe profile and was well tolerated.[23]

The phase III BREEZE-AD1 and BREEZE-AD2 trials were conducted in adults randomized to four QD treatment arms.[24] According to these trials, AEs were reported in 56%, 58%, 54%, and 55% and SAEs in 1.2%, 1.2%, 4%, and 3% of those receiving 4 mg baricitinib, 2 mg baricitinib, 1 mg baricitinib, or placebo, respectively. There were no deaths or reported cases of venous thromboembolism, cardiovascular events, gastrointestinal perforation, or significant hematological changes. In both studies, the most commonly reported AEs were headache and nasopharyngitis.

Conclusions

The JAK–STAT signaling pathway is fundamental in regulating immune function. JAK inhibitors target several inflammatory pathways at once and improve the signs and symptoms of complex conditions, including AD. The selectivity of agents allows for interaction with some JAK isoforms over others. Clinical trials exploring the safety and efficacy of the oral JAK inhibitors abrocitinib, baricitinib, and upadacitinib in the treatment of AD have so far shown promising results in both adolescents and adults. Low rates of AEs and rapid relief of pruritus and the clinical signs of AD will make these agents a welcome addition to our toolbox of therapeutic options in managing this debilitating condition. Currently, the monoclonal antibody dupilumab, targeting IL-4Rα, which blocks IL-4 and IL-13, is approved for moderate-to-severe AD and will be the main competitor.[25] Each has their advantages, as some patients prefer a subcutaneous injection with no laboratory monitoring, whereas others may prefer the convenience of oral therapy. The rapid and clinically significant improvement of pruritus with JAK inhibitors may be a deciding factor for some. Additionally, dupilumab failures will now have another option with oral JAK inhibition, and vice versa. Continued investigations into JAK inhibitors are required to determine the long-term safety, efficacy, and maintenance of response of this therapeutic class in both adolescents and adults. Long-term extension studies should meet this need. How these agents compare to each other is not known as head-to-head trials are yet to be conducted. Although IGA response rates seem higher for abrocitinib and upadacitinib compared to baricitinib, conclusions cannot be drawn due to differences in study design. The clinical significance of these differences will become apparent with real-world use or future head-to-head trials. What is important for the clinician and the patient is that more treatment options will become available for those suffering from AD.

Further characterization of the safety of the JAK inhibitor class is needed to better understand the risks of venous thromboembolism, malignancy, and infection rates. JAK selectivity may reduce associated AEs by avoiding the blockade of isoforms not involved in control of disease. Although dupilumab has an excellent safety profile, there are cases of conjunctivitis and injection site reactions that are not seen with the JAK inhibitor class. If these early promising results are confirmed with long-term data, this group of drugs may be the 'JAKpot' for primary or secondary therapy in the treatment of moderate-to-severe AD in the future.

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